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PRACTICAL ISSUES AND UPDATES

COVID-19: State of the Vaccination

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Abstract
The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting coronavirus disease 2019 (COVID-19) pandemic has led to rapid vaccine development and emergency use (EU) rollout. Six vaccines, including two using novel mRNA technology, are EU-listed by the World Health Organisation, and promising published trial data are available for nine more. While efficacy is good, there are various barriers to their global use. Long-term safety and immunogenicity data are being collected along the way.

Many aspects define future-fit SARS-CoV-2 vaccines

Since wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in China in 2019, the resulting coronavirus disease 2019 (COVID-19) pandemic has prompted the rapid development, emergency use listing or approval (EUL or EUA) and rollout of vaccines [1, 2]. This paper summarises promising COVID-19 vaccines as of 7 September 2021, based on available data, with emphasis on published phase 3 trial results. Data are sourced from peer-reviewed journals, press releases, public health organisations such as the World Health Organisation (WHO), the European Medicines Association (EMA) and the US Communicable Diseases Centre (CDC), review articles (Kyriakidis et al, McDonald et al and Sadarangani et al. [1, 3, 4]) and vaccine tracking websites [2, 5].

An ideal vaccine provides long-term protection in all populations after one dose, and is safe, affordable and easy to mass manufacture, store and distribute [1]. It must also be accepted; at present, WHO includes vaccine hesitancy (outside of the scope of this article) in its top 10 threats to global health [6]. While scientific opinions initially predicted that it would take at least a year to a year and a half for a COVID-19 vaccine to be approved for use in the USA, advances in the field allowed the issuing of EUAs for various vaccines by national and international drug regulation agencies within a year of the SARS-CoV-2 genome sequence being released [4]. By 7 September 2021, six COVID-19 vaccines had received WHO EULs, one of which (the AstraZeneca/University of Oxford formulation) has two versions (Vaxzevria™ and Covishield™, the latter manufactured by the Serum Institute of India) (Tables 1, 2). Nine more vaccines (Table 3) had published acceptable or excellent phase 3 efficacy results and ≥ 20 others had reached phase 3 trials (Table 5) [2, 5]. However, among the plethora of potential efficacious options, few meet the various ideal-vaccine [1] criteria.

Varied technology, varied pros and cons

Some vaccine technologies are well established [e.g. inactivated or live-attenuated whole virus, or viral subunit (protein or virus-like particles)], but COVID-19 vaccines have employed technologies such as novel modified viral mRNA or DNA approaches [4] and adenovirus (AD) vectors, generally with good efficacy (Tables 1, 3) [4, 7]. Immunology (Table 4) is not yet clear, but predictable issues with various technologies include:

- inactivated, non-replicating virus and protein subunit vaccines (e.g. Sinovac's CoronaVac and Sinopharm's BBIBP-CorV) usually need booster shots and/or adjuvants as they typically prompt either no, or a weak, short-lived cellular immune response [4, 7];
- potential reversion to virulent or wild-type strains mean all whole virus vaccines need regular testing [7];

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Table 1 SARS-CoV-2 (COVID-19) vaccines with World Health Organisation (WHO) emergency use listing as at 7 Sep 2021 [2, 4, 9, 10]

Vaccine (company developing)	Key information
mRNA-1273; TAK-919 (Moderna/National Institute of Allergy and Infectious Diseases/Takeda)[a]	
Name (brand name): dosage	Elasomeran (Spikevax®) IM: 2 × 0.5 mL (100 µg) doses 4 wks apart
Class of vaccine	Modified mRNA encapsulated in lipid NP vector, encoding full-length S protein [3, 4]
Approvals/EUAs: patient populations	Approved in Switzerland and EUA in European Union, Japan, UK, USA and > 30 other countries [2]: adults and adolescents aged >12 y (e.g. European Union) or adults aged ≥ 18 y (e.g. USA)
Storage	Stable at −20 °C for ≤ 6 mo and 2–8 °C for 30 d [4]
Cost per dose/doses available (2021)	US $15 in USA, $18 in EU [9]/800M leaving 860M shortfall vs orders [10][b]
BNT162b2 (BioNTech/Pfizer/Fosun Pharma)[a]	
Name (brand name): dosage	Tozinameran (Comirnaty®) IM: 2 × 0.3 mL (30 µg) doses 3 wks apart
Class of vaccine	Modified mRNA encapsulated in lipid NP vector, encoding full-length S protein [3, 4]
Approvals/EUAs: patient populations	Approved in USA, Switzerland, Bahrain, Brazil, New Zealand and Saudi Arabia, EUA in European Union and > 50 other countries [2]: mostly adults and adolescents aged ≥ 12 y (US full approval in ≥ 16 y and US EUA in ≥ 12 y)
Storage	Stable at −60 °C; 2–8 °C for 1 mo [11]
Cost per dose/doses available (2021)	US $19.50 for first 200M doses in USA, $14.70 in EU [9]/3B leaving 580M shortfall vs orders [10][b]
AZD1222; Covishield (AstraZeneca/University of Oxford/Serum Institute of India)[a]	
Name (brand names): dosage	ChAdOx1-S (Vaxzevria™; Covishield™ manufactured by Serum Institute of India) IM: 2 × 0.5 mL (≥ 2.5 × 10^8 InfU = 5 × 10^{10} VP) doses 4–12 wks apart
Class of vaccine	Recombinant debilitated chimpanzee AD OX1 vector DNA expressing full-length S protein [3, 4]
Approvals/EUAs: patient populations	Approved in Brazil, EUA in European Union, Argentina, UK and > 50 other countries (not USA): adults aged ≥ 18 y; permanently stopped in Denmark and Norway [2]
Storage	Stable at 2–8 °C
Cost per dose/doses available (2021)	US $2.15 in EU, $3 in UK, $4 in USA [9]/2.1B, with 1.1B shortfall vs orders [10][b]
Ad26.COV2.S; JNJ-78436735 (Janssen of Johnson & Johnson/Beth Israel Deaconess Medical Centre)[a]	
Name (brand name): dosage	COVID-19 Vaccine Janssen [Ad26.COV2-S (recombinant)] IM: 1 × 0.5 mL dose (≥ 8.92 $\log_{10}$ InfU = 5 × 10^{10} VP) [12]
Class of vaccine	Recombinant, debilitated human AD 26 vector expressing stabilised prefusion full-length S protein [3, 4]
Approvals/EUAs: patient populations	EUA in European Union, UK, USA and > 30 other countries: adults aged > 18 y Vaccine rollout stopped in Denmark, Finland and restricted to volunteers in Norway [2]
Storage	Stable at 2–8 °C
Cost per dose/doses available (2021)	US $10, $8.50 in EU [9]/500M, with 395M shortfall [10][b]
CoronaVac (Sinovac R&D)[a]	
Name: dosage	CoronaVac IM: 2 × 3 µg doses 2 wks apart
Class of vaccine	Inactivated whole SARS-CoV-2 grown in Vero cells, aluminium hydroxide adjuvant [4, 13]
Approvals/EUAs: patient populations	Approved in China (people aged ≥ 3 y); EUA in > 30 countries: WHO EUL for adults aged ≥ 18 y; use stopped in Malaysia
Storage	Stable at 2–8 °C
Cost per dose/doses available (2021)	US $29.75 in China /1.75B, with 751M spare capacity
BBIBP-CorV COVID-19 vaccine [Sinopharm; China National Biotec Group (CNBG)][a]	
Name: dosage	SARS-CoV-2 Vaccine (Vero Cell) IM: 2 × 0.4 µg doses 2–4 wks apart [14]
Class of vaccine	Inactivated whole SARS-CoV-2 (HB02 strain) grown in Vero cells, aluminium hydroxide adjuvant [4]
Approvals/EUAs: patient populations	Approved in China (aged ≥ 3 y), Bahrain, UAE; EUAs in Hungary and > 40 others: adults aged ≥ 18 y
Storage	Stable at 2–8 °C
Cost per dose/doses available (2021)	US $19–36 [15], $30 in China/1B, with 645M spare capacity [10][b]

AD adenovirus, *B* billion, *d* day, *EUA/L* emergency use authorisation/listing, *h* hour(s), *IM* intramuscular, *InfU* infectious units, *M* million, *mo* months, *NP* nanoparticle, *S protein* SARS-CoV-2 spike protein, *VP* viral particles, *vs* versus, *wk(s)* week(s)

[a]Approval and/or EUA in countries meeting WHO stringent regulatory authority criteria

[b]Manufacturing capacity is for 2021, while some orders may be for 2022, so shortfalls may not eventuate [10]

- mRNA is very unstable, necessitating freezer storage of the Moderna mRNA-1273 and Pfizer BNT162b2 vaccines (Table 1), and booster doses are probably needed [2, 7];
- DNA vaccines could potentially integrate into the human genome, and probably need booster shots [7];
- the efficacy and tolerability of AD vector vaccines can be affected by recipients' previous exposure and anti-

bodies (Abs) to common ADs, although this risk has been mitigated by the use of chimp AD (e.g. AstraZeneca's AZD1222; Table 1), rare human AD26 (Janssen's Ad26.COV2.S, [4]; Table 1) and different AD vectors in doses one and two (Gamaleya's Sputnik vaccines; Table 3); and
- novel technologies may cost more and increase vaccine hesitancy [6].

Although proven, eventually cheap to make and conferring long-lasting immunity, live-attenuated viruses (used, e.g., to prevent measles) seem unsuited to the COVID-19 pandemic, as they may take years to develop, do not suit fast-changing viruses and may be affected by coronavirus cross-immunity [4].

WHO approval linked to COVAX, others are needed

Equitable distribution of vaccines is proving difficult and the COVID-19 Vaccines Global Access (COVAX) initiative, co-led by WHO, aims to provide doses to lower-income countries [8]. However, COVAX may only distribute vaccines with WHO EULs (Table 1) [8] and the six that qualify so far are not logistically ideal. All are IM formulations requiring frozen or refrigerated storage, most are expensive and all but one require two initial doses (Table 1) [4, 8].

Good efficacy, especially for severe COVID-19

Several WHO EUL vaccines demonstrate ≥ 75% efficacy against symptomatic COVID-19 infection, and all showed excellent efficacy against severe illness (Table 2) [14]. Longer-term safety data now reveal anaphylaxis and very rare, but serious, vaccine adverse events (e.g. myocarditis, predominantly affecting men aged < 30 years, with the mRNA vaccines; thrombosis with thrombocytopenia syndrome, most common in women aged < 55 years and 30–49 years with the ChAdOx1 and Ad26.COV2.S vaccines, respectively [16, 17]) [Table 2], leading to some rollout reviews (Table 1). More positively, after the administration of well over 180 and 133 million doses of the BNT162b2 and mRNA-1273 vaccines, BNT162b2 has now received full US FDA approval [18] and Moderna has filed for full approval for mRNA-1273 [19].

Pregnant women and children last…

Only the BNT162b2 vaccine is WHO-listed for adolescents (Table 2), but increased COVID-19 knowledge confirms children and adolescents, as well as pregnant women, need safe vaccines. Several developments are in progress:

- Moderna is seeking FDA approval for people aged ≥ 12 years, as its TeenCOVE phase 2/3 study in 3732 adolescents met its primary endpoint of non-inferior immunogenicity versus that in adult comparators (vaccine efficacy 100%) [29];
- Pfizer, Moderna and China National Biotec Group with Beijing Institute of Biological Products (CNBG/BIBP) have all registered Phase 2/3/4 trials in children aged 6 months to 12 years (Moderna; NCT04796896/KidCOVE, and Pfizer; NCT04816643), those aged 3 to 17 years (CNBG/BIBP; NCT04863638, NCT04917523) or adolescents (Pfizer dose-boost study; NCT04368728) [30];
- Phase 2/3 studies in younger people have been registered for the non-WHO EUL vaccines (Table 3) Covaxin (ages 2–18 years), Sputnik V and Novavax NVX-CoV2373 (both ages 12–17 years) [30]; and
- Pfizer is conducting a phase 2/3 study of the BNT162b2 vaccine in pregnant women (NCT04754594) [30].

While preliminary US surveillance system and registry data have not revealed any obvious safety signals among pregnant women administered mRNA COVID-19 vaccines, more extensive long-term data are needed [31].

… along with immunocompromised patients

Immunocompromised patients, including those with autoimmune disorders or on immunosuppressive medications, have typically been excluded from vaccine trials and require particular attention, given that infections are a common cause of mortality in this group [32]. Although further research is warranted to determine the effects of immunocompromising medical conditions and immunosuppressing medications on COVID-19 vaccine efficacy, the benefits of vaccination are expected to outweigh any possible risks [33]. Additional doses may be required to achieve adequate protection; in August 2021, the US FDA approved an update to the EUAs for BNT162b2 and mRNA-1273 to include a third dose for certain immunocompromised patients [34].

Table 2 Efficacy and safety in randomized, placebo-controlled, multicentre phase 3 trials of SARS-CoV-2 (COVID-19) vaccines with WHO emergency use listing at 7 Sep 2021 [14]

Phase 3 trial	Results
mRNA-1273, TAK-919, elasomeran (Spikevax®): Moderna/National Institute of Allergy and Infectious Diseases/Takeda	
COVE trial: regimens [20]	> 30,000[a] US adults: 2 × 0.5 mL (100 µg) IM doses mRNA-1273 or PL, both 28 d apart
Demographics (BL)	5% Asian, 10% Black, 79% White, 21% Hispanic, 25% aged ≥ 65 y (mean 51 y), mean BMI 29
Efficacy: PE[b] (n = 28,207)[a]	94.1% (95% CI 89.3–96.8%) [21]
Other endpoints/subgroups	SCH 100%; those aged ≥ 65 y 86.4%; race, sex, and presence of risk for severe COVID-19 all 90.9–97.5% [20]
Safety (n = 30,351)[a]	Common ADEs: ISP (> 90%), fatigue (70%), headache, myalgia (> 60%), arthralgia, chills (> 40%), nausea/vomiting (> 20%), axillary swelling/pain, fever or ISR (> 10%) [20, 21] Serious/severe ADEs: Bell's palsy in 3 vaccine and 1 PL recipient, facial swelling in 2 vaccine recipients with dermatological fillers, severe nausea/vomiting in 1 vaccine recipient [20]
Post-trial surveillance	Mild myocarditis and pericarditis, especially in young male adults and adolescents [21]
BNT162b2, tozinameran (Comirnaty®): BioNTech/Pfizer [11, 22]	
NCT04368728: regimens	> 43,000[a] people, 77% in USA, aged ≥ 16 y: 2 × 0.3 mL (30 µg) doses IM Comirnaty or PL, 21 d apart Additional analysis in 2,260 adolescents aged 12–15 y [23], with similar demographics
Demographics (PPS)	5% Asian, 9% Black, 83% White, 27% Hispanic, 22% aged ≥ 65 y (median 52 y), 46% with comorbidity[c]
Efficacy: PE[b] (n = 36,523 SN at BL, 40,137 SN or SP at BL)[a]	95.0% (95% CI 90.3–97.6%) in those SN at BL [22] 94.6% (95% CI 89.9–97.3%) in those SN or SP at BL [22]
Other endpoints/subgroups	SCH 75%; people aged ≥ 65 y/75 y 94.7/100%; 2,230 SN or SP adolescents aged 12–15 y 100%; by race, gender, and in Argentina, Brazil and USA all 89–97% [14]
Safety (n = 37,586)[a]	Common ADEs: ISP/R (> 80%), fatigue (> 60%), headache (> 50%), myalgia, chills (> 30%) arthralgia (20%), fever (> 10%) [11]; ADEs similar, but slightly more common in adolescents [24] 4 cases Bell's palsy in vaccine group [11, 24], insufficient data for conclusion
Post-trial surveillance	Mild myocarditis and pericarditis especially in young male adults and adolescents
ChAdOx1-S recombinant IM injection (Vaxzevria™, Covishield™): AstraZeneca/University of Oxford [25]	
COV 001, 002, 003 and 005: regimens	> 24,000[a] adults in UK, Brazil and South Africa: 2 × 0.5 mL (≥ 2.5×10^8 InfU = 5×10^{10} VP) IM doses ChAdOx1-S or PL 4–12 wks apart [3, 25]
Demographics (BL)	71% White, 12% Black (↓ to 6% in PPS), 3% Asian, 39% with comorbidity[c], 13% ≥ 65 y
Efficacy: PE[b] (n = 14,380)[a]	COV 002 (UK) and 003 (Brazil): 59.5% (95% CI 45.8–69.7%)
Other endpoints/subgroups	SCH 100% after 1 or 2 doses; any dose interval (21–159 d) 62.6% [25]; those with comorbidity[c] 58.3%
Safety (n = 23,745)[a]	Common ADEs: ISP/R (> 60%), headache, fatigue (> 50%), myalgia, malaise (> 40%), pyrexia, chills (> 30%), arthralgia, nausea (> 20%), fever ≥ 38 ℃ (7.6%)
Post-trial surveillance	Very rare: TTS, mostly in women aged < 60 y, CLS (some in people with CLS history), GBS [25]
Ad26.COV2.S; JNJ-78436735 (Janssen of Johnson & Johnson/Beth Israel Deaconess Medical Centre) [12, 26]	
COV 3001 trial: regimens	> 44,000[a] adults in Latin America, South Africa and the USA: 1 × 0.5 mL (≥ 8.92 $\log_{10}$ InfU = 5×10^{10} VP) dose IM Ad26.COV2.S or PL [27]
Demographics (PPS)	41% Latin America, 13% South Africa, 47% US, 20% aged ≥ 65 y (median 52 y), 40% comorbidity
Efficacy: PE[b] (n = 39, 321)[a]	Moderate/severe COVID-19 14 d post-vacc: 66.9% (95% CI 59.0–73.4%) in SN or unknown BL serostatus Moderate/severe COVID-19 28 d post-vacc: 66.1% (95% CI 55.0–74.8) in SN or unknown BL serostatus
Other endpoints/subgroups	SCH 76.7% and 85.4% 14 and 28 d post-vacc; age ≥ 60 y (any COVID-19) 76.3% and 66.2% 14 d and 28 d post-vacc; Brazil, South Africa and USA all 64–72% for COVID-19 and 82–88% for SCH at 28 d post-vacc
Safety (n = 43,783)[a]	Common ADEs: IS pain (> 40%), headache, fatigue, myalgia (> 30%), nausea (> 10%), fever ≥ 38 ℃ (9%)
Post-trial surveillance	Very rare: TTS, mostly in women aged < 60 y, GBS, mostly in men aged ≥ 50 y [12]

Table 2 (continued)

Phase 3 trial	Results
CoronaVac (Sinovac R&D)	
PROFISCOV trial: regimens Turkey trial: regimens	> 12,500[a] adult HCW in Brazil (pre-P.1 variant): 2 × 0.5 mL (3 µg) IM doses CoronaVac or PL 14 d apart > 10,000[a]: HCW + others aged 18–59 y, randomised 1:1 (HCW) or 2:1 (others) to: 2 × 0.5 mL (3 µg) IM doses CoronaVac or PL 14 d apart
Demographics (BL)	Brazil: 5% aged ≥ 60 y (mean 39.5 y), 36% male, 89.9% SN at BL, 10.1% SP at BL Turkey: 36% HCWs, 58% male, 16% obese (BMI ≥ 30[c]), median BMI 25.7, median age 45 y
Efficacy: PE[b] (n = 9823 in Brazil [14], 10,029 in Turkey[a] [28])	Brazil: 50.7% (95% CI 35.9–62.0%) Turkey: 83.5% (95% CI 65.4–92.1%)
Other endpoints/subgroups:	Brazil: SCH efficacy not shown, ↑ dose interval (21–28 d) 62.3% (95% CI 13.9–83.5); 60.4% at ≤ 56 d post-dose, waned to 52.5% (51.9–53.1) at ≤ 98 d post-dose Efficacy not shown in males, those aged ≥ 60 y or with comorbidities[c], or dose interval < 21 d Turkey: SCH 100% in young, healthy population [28]
Safety (n = 12,396 in Brazil, 10,214 in Turkey)[a] [14]	Common ADEs: ISP, ISR, headache, fatigue, myalgia Serious/severe ADEs: Anaphylaxis in 1 vaccine recipient in Turkey
Post-trial surveillance	After ≈ 36M doses in China, 49 serious ADEs including anaphylactic shock (6 cases), Henoch-Schönlein purpura (5 cases), facial paralysis (4 cases), laryngeal oedema, demyelination, cerebral haemorrhage (3 cases each) and GBS (2 cases)
BBIBP-CorV COVID-19 vaccine [Sinopharm; China National Biotec Group (CNBG)][a] [14]	
COVIV-02: regimens	3-way trial in > 41,000[a] adults in Bahrain, Egypt, Jordan, UAE randomised 1:1:1[a] to BIBP, or a second vaccine WIBP, or PL: BIBP dosage 2 × 4 µg IM doses 21 d apart
Demographics (safety data)	98% < 60 y, 85% male, 22.2% obese[c], 13% Chinese, 87% Asian [14]
Efficacy: PE[b] (n = 27,536, excluding WIBP group)[a]	78.1% (95% CI 64.8–86.3) (PE[b] does not specify SN) [14]
Other endpoints/subgroups	78.1–80.8% in SN at BL, those aged < 60, with BMI ≥ 30[c] and males [14]
Safety (n = 29,237)[a]	Common ADEs: ISP, headache, fatigue Serious ADEs: nausea, inflammatory demyelination syndrome possibly linked to BIBP, thrombus (each in one patient)
Post-trial surveillance	5.9M BBIBP-CorV recipients, China: facial nerve symptoms (n = 11), fever ≥ 38.6 ℃ (n = 86)

ADE(s) adverse drug event(s), *BL* baseline, *BMI* body mass index in kg/m^2, *CLS* capillary leak syndrome, *d* day, *GBS* Guillain-Barre syndrome, *HCW* healthcare workers, *IM* intramuscular, *InfU* infectious units, *ISP/R* injection-site pain/reaction, *mo* month(s), *PE* primary endpoint, *PL* placebo, *post-vacc* post-vaccination, *PPS* per-protocol set, *SCH* severe COVID-19 and/or hospitalisation, *SN* seronegative, *SP* seropositive, *TTS* thrombosis with thrombocytopaenia syndrome, *wk(s)* week(s), ↑ increased

[a]Unless otherwise indicated, participant numbers are: for trial, those randomised 1:1 vaccine:PL; for efficacy analysis, PPS for vaccine and PL; and for safety analysis, those who received ≥ 1 dose of vaccine or PL; some safety analyses are from combined trial results

[b]Unless otherwise stated, prevention of laboratory-confirmed, symptomatic COVID-19 in those SN at BL, with onset > 7 d (BNT162b2 vaccine), > 14 d (mRNA-1273, ChAdOx1-S, Ad26.COV2.S, CoronaVac, BBIBP-CorV vaccines) and/or 28 d (Ad26.COV2.S vaccine) post-dose 2

[c]Comorbidities associated with an increased risk of severe COVID-19

Other promising vaccines yet to be WHO-listed

Table 3 shows currently COVAX-ineligible vaccines with reported phase 3 trial efficacy of 62–93%, plus other benefits [2, 35]. Two are stable for weeks at room temperature (Table 3), and two developed in India (one needle-free) appear effective against the delta strain [36]; the phase 3 trial of the needle-free ZyCoV-D vaccine also included adolescents [36]. Most of these vaccines are already in use (Table 3) [2, 5].

Understanding of immunogenicity just beginning…

Understanding the immunological mechanisms of current vaccines, the related correlates of protection (COPs) and the durability of immunity is essential to optimise the efficacy and practicality of COVID-19 vaccines and limit the development of viral "escape mutants" [1, 3]. At present, immunological data are short-term and very limited, trial assays vary and immunogenicity is not well understood [3, 40]. Questions around the need for booster doses, the ideal dose

Table 3 SARS-CoV-2 (COVID-19) vaccines with reported phase 3 results, but without WHO emergency use listing at 7 Sep 2021 [2, 9, 10, 13]

Vaccine (company developing)	Key information
ZyCoV-D (Zydus Cadila Healthcare, India)[a]	
Type of vaccine	Non-replicating and non-integrating plasmid DNA encoding S protein
Formulation (brand name): dosage	Intradermal, applied via The PharmaJet® needle-free Tropis® system: 3 × 3 mg doses, 4 wks apart
Reported efficacy	66.6% for symptomatic COVID-19, including in adolescents (via company press release) [36]
Approvals/EUAs: patient populations	EUA in India: phase 3 trial in adults and 1000 adolescents aged 12–18 y
Other considerations	Stored at 2–8 °C, but stable at 25 °C for 3 mo; 2021 mfg target 100M doses, all available
Sputnik; Gam-Covid-Vac (Gamaleya Research Institute and Health Ministry of the Russian Federation)	
Type of vaccine	Replication-deficient human AD5 (dose 1) and AD26 (dose 2) vector expressing S protein [13]
Formulation (brand name): dosage	IM Gam-Covid-Vac (Sputnik V or Light): 2 × 0.5 mL (10^{11} VP [3]) doses 3 wks apart (Light = 1 dose)
Reported efficacy	Sputnik V: 91.6% in peer-reviewed journal, but sufficiency of data questioned [37]
Approvals/EUAs: patient populations	EUA in > 70 countries: adults
Other considerations	Liquid/freeze-dried stable at −18 °C/2–8 °C; CPD ≤ US$10; 2021 mfg target ≈ 390M doses, with 58M shortfall vs orders[b]
AD5-nCoV (CanSino Biologics, Beijing Institute of Biotechnology and Chinese Academy of Military Medical Sciences)[a,c]	
Type of vaccine	Recombinant human AD type 5 vector DNA expressing full-length S protein [3, 13]
Formulation (brand name): dosage	IM AD5-nCoV (Convidecia): single 5 × 10^{10} VP dose [13]
Reported efficacy	65.3% (via media reports)
Approvals/EUAs: patient populations	Approved in China, EUA in Latin America, Hungary, Malaysia, Mexico, Moldova, Pakistan: adults
Other considerations	Stable at 2–8 °C + for 3 wks at RT; CPD US$27 [15]; 2021 mfg target 500M doses, with 359M available
NVX-CoV2373 (Novavax), manufactured as Covovax (Serum Institute of India)	
Type of vaccine	Prefusion recombinant full-length S protein NP + saponin-based Matrix-M1™ adjuvant [3, 4]
Formulation (brand name): dosage	IM NVX-CoV2373 (Covovax): 2 × (5 µg protein + 50 µg adjuvant) doses, 3 wks apart
Reported efficacy	89.7% for symptomatic COVID-19, 86.3% against α variant (via peer-reviewed journal) [35]; may be less effective against β variant
Approvals/EUAs: patient populations	Plans to apply to US FDA for EUA in 4th quarter (applications filed in India, Indonesia, Philippines)
Other considerations	Stable at 2–8 °C; CPD US$16 in USA; 2021 mfg target 580M doses, with shortfall of 939M[b]
CIGB-66 (Center for Genetic Engineering, Cuba)[a]	
Type of vaccine	Protein subunit (receptor-binding domain of S glycoprotein) + aluminium hydroxide
Formulation (brand name): dosage	IM CIGB-66 (Abdala): 3 × 50 µg doses 2 wks apart
Reported efficacy	92.28% (via media reports)
Approvals/EUAs: patient populations	EUA in Cuba and Venezuela
Other considerations	Stable at 2–8 °C [38]
BBV152 (Bharat Biotech and Indian Council of Medical Research, Ocugen USA)	
Type of vaccine	Inactivated SARS-CoV-2 grown in Vero cells + aluminium hydroxide adjuvant + imidazoquinoline molecule [3]
Formulation (brand name): dosage	IM BBV152 (Covaxin™): 2 × 6 µg doses 28 d apart
Reported efficacy	77.8% against symptomatic COVID-19, 93.4% against severe COVID-19 (article preprint)
Approvals/EUAs: patient populations	EUA in India and > 10 other countries, seeking full approval from US FDA, use stopped in Brazil [2][b]
Other considerations	Stable at 2–8 °C, RT for 1 wk; CPD ≈ US$3; 2021 mfg target 590M doses, with 537M shortfall[b]
WIBP COVID-19 (Vero) vaccine (Sinopharm, Wuhan Institute of Biological Products and Beijing Institute of Biological Products)	
Type of vaccine	Inactivated SARS-CoV-2 grown in Vero cells with aluminium hydroxide adjuvant [4]
Formulation: dosage	IM WIBP Cor-V: 2 × 5 µg doses 21 d apart
Reported efficacy	72.8% (WIV04 strain group) and 78.2% (HB02 strain group) [initial report in peer-reviewed journal] [39]
EUA/approvals: patient populations	Approval in China, limited use in UAE
Other considerations	Stable at 2–8 °C

Table 3 (continued)

Vaccine (company developing)	Key information
ZF2001 (Anhui Zhifei Longcom Biologic Pharmacy)[a]	
Type of vaccine	Protein subunit (receptor-binding domain of S protein) with aluminium hydroxide adjuvant
Formulation (brand name): dosage	(Zifivax) IM: 3 × 25 μg doses 4 wks apart
Reported efficacy	81.76% (100% against severe cases and death, 77.54% against δ variant; via media reports)
EUA/approvals: patient populations	EUA in China and Uzbekistan
Soberana 2 (Instituto Finlay de Vacunas)[a]	
Type of vaccine	Protein subunit (receptor-binding domain of S protein) with aluminium hydroxide adjuvant
Formulation (brand name): dosage	IM FINLAY-FR-2; Soberana 2 (Pasteur in Iran), Soberana Plus (booster): IM 2 (Soberana 2) or 3 (Soberana Plus) × 25 μg doses 28 d apart
Reported efficacy	62% with two doses, 91.2% with Soberana Plus (via media reports)
EUA/approvals: patient populations	EUA for Soberana 2 and Soberana Plus in Cuba; EUA of Soberana 2 (Pasteur) in Iran

AD adenovirus, *d* day(s), *CPD* cost per dose, *EUA* emergency use authorisation, *FDA* Food & Drug Administration, *h* hour(s), *IM* intramuscular, *mfg* manufacturing, *NP* nanoparticle, *RT* room temperature, *S* SARS-CoV-2 spike, *VP* viral particles, *wk(s)* week(s), *y* year(s)

[a]Initial press release only, no results published in peer-reviewed journal

[b]Manufacturing capacity is for 2021, while some orders may be for 2022, so shortfalls may not eventuate [10]

[c]EUA in Hungary, which meets WHO stringent regulatory authority criteria

interval, and mucosal immunity and responses are largely unanswered [3].

… but humoral and cell-mediated immunity involved

The genome of SARS-CoV-2 encodes the spike (S) protein (among others), which includes the S1 subunit containing the receptor-binding domain (RBD) and the S2 subunit that mediates membrane fusion and cell entry [7]. SARS-CoV-2 uses the RBD to engage with the host cells' receptor angiotensin-converting enzyme 2 (ACE-2). The S protein can trigger both humoral and cell-mediated (i.e. neutralising Abs and T- and B-cell) immune responses [7]; both types appear to mediate recovery from COVID-19 infection (Table 4 [3]).

Most vaccines are designed to generate neutralising Abs (NAbs) against S proteins (Table 4), with several studies identifying a strong correlation between vaccine efficacy and mean NAb, even at very low NAb levels [13]. For example, the vaccine-generated NAb levels for 50% and full protection against detectable COVID-19 were 20.2% and 28.6% of the mean convalescent level and 50% protection against severe COVID-19 occurred at 3.0% [13]. After two doses, both mRNA and AD-vectored vaccines elicit NAb levels equivalent to, or higher than, those of patients who are in convalescence (with NAb levels relative to those in convalescent plasma being somewhat greater with mRNA vaccines than with AD-vectored vaccines) [3].

However, other evidence and experience with other coronavirus infections, e.g. SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), strongly suggest that NAbs alone are unlikely to provide such significant immunity [3, 40]. Cellular immunity, non-neutralising Abs and innate mechanisms, e.g. type I and II interferons, are all likely to be involved [3, 40].

The many functions of cytotoxic T-cells include recognising and killing infected cells, releasing cytokines and supporting the antibody response of B-cells [3, 40]. Clinical evidence for their involvement in COVID-19 immunity includes milder or asymptomatic infection in people with a strong T-cell response [3, 40] and the presence of T-cells in people with undetectable SARS-CoV-2 Abs [40]. More T-cell data are needed [40]. The NAb titre also correlates with anti-RBD immunoglobulin (Ig)G levels [7] and Ab activity in this region is also of interest (Table 4 [3]).

Very virulent variants may still respond

Vaccines were initially developed for protection against COVID-19 strains identified in Wuhan, China, but SARS-CoV-2's fast mutation rate means efficacy against more transmissible variants of concern (VOCs) and perhaps additional variations of interest is required [41]. VOCs are:

- alpha (α, or B.1.1.7 +/- E484K), which spreads faster and may cause more severe illness;
- beta (β or B.1.351);
- gamma (γ or P.1), which spreads faster; and
- delta (δ or B.1.617.2), which spreads much faster and may cause more severe illness, now present in almost 100 countries.

Table 4 Immunogenicity of SARS-CoV-2 (COVID-19) vaccines with published data in humans, as reviewed by Sadarangani et al [3]

Vaccine (brand name): dosage regimen[a]; efficacy[b]	Neutralising Ab response	Binding Ab response	T-cell response
Vaccines with World Health Organisation (WHO) emergency use listing as of 7 September 2021			
mRNA-1273 Elasomeran (Spikevax®): 2 × 100 µg mRNA doses 4 wks apart; 95%	Minimal NAb after dose 1, peak 14 d after dose 2	S-BAb 14 d after dose 1, slight ↑ at 28 d, marked ↑ after dose 2	Small/significant ↑ in $CD4^+$ cells secreting T_H1 cytokines after dose 1/2, little T_H2 or $CD8^+$ response
BNT162b2 Tozinameran (Comirnaty®): 2 × 30 µg mRNA doses 3 wks apart; 95%	Significant NAb only after dose 2	Some S-BAb after dose 1, ↑ after dose 2	After dose 2, ↑ IFN-γ, antigen-specific $CD4^+$ and $CD8^+$ T cells, likely T_H1 polarisation[c]
ChAdOx1-S (Vaxzevria™, Covishield™): 2 × (5.0×10^{10} VP) doses ≥ 4 wks apart; 62–67%	Significant NAb after dose 1, ↑ by 14 d after dose 2	S-BAb 14 d after dose 1, slight ↑ at 28 d, marked ↑ after dose 2	After dose 1, peak TCR at 14 d, but ↑ 28 d after dose 2 ↑ TNF and IFN-γ production by $CD4^+$ T cells at day 14
Ad26.COV2-S (recombinant): 1 × (5×10^{10} VP) dose; 67%	NAb in 99% by 28 d post-dose, Ab levels sustained at ≥ 84 d post-vacc	S-BAb in 99% by 28 d post-dose, Ab levels sustained at ≥ 84 d post-vacc	$CD4^+$ and $CD8^+$ TCRs at 14 d and 28 d post-vacc, likely T_H1 polarisation[c]
CoronaVac: 2 × 3 µg protein doses 2 wks apart; 50–84%	NAb in ≥ 94% 28 d after dose 2	By day 28, RBD BAb in ≥ 88% and ≥ 99% after 14 d and 28 d dose intervals	Not reported
BBIBP COVID-19 Cor-V: 2 × 0.4 µg protein doses 21 d apart; 86%	NAb in 100% by 21 d after dose 2	BAb in 46–87% and 92–100% at 14 d and 28 d after dose 2	Not reported
Vaccines with reported efficacy and immunogenicity [3], without WHO emergency use listing as of 7 September 2021			
Gam-Covid-Vac (Sputnik V): 2 × 10^{11} VP doses 3 wks apart; 91%	NAb in 61% and 95% 14 d after doses 1 and 2	S-BAb in 85–89% 14 d after dose 1 and 98% 14 d after dose 2	$CD4^+$ and $CD8^+$ TCR 14 d after dose 1, S-specific IFN-γ responses in 100% 7 d after dose 2
AD5-nCoV (Convidecia): Single 5 × 10^{10} VP dose; 66%	NAb in 47–50% by 28 d post-vacc, ↓ NAb if pre-existing AD5 Ab titre > 1:200	RBD BAb in 44% and 97% 14 d and 28 d post-vacc ↓ BAb if pre-existing AD5 Ab titre >1:200	TCR in 78–88% 28 d post-vacc; peak at 14 d post-vacc
NVX-CoV2373 (Covovax): 2 × 5 µg protein doses 3 wks apart; 90%	Some NAb after dose 1, marked ↑ 7 d after dose 2	S-BAb 21 d after dose 1, marked ↑ after dose 2	$CD4^+$ TCR by 7 d after dose 2, strong T_H1 bias[c]
BBV152 (Covaxin™): 2 × 6 µg protein doses 4 wks apart; 78%	NAb in 48% after dose 1 and 97%, with ↑ titres, by 14 d after dose 2	S-BAb in 65% after dose 1, and 98%, with ↑ titres, 14 d after dose 2	Strong T_H1 bias[c], ↑ some memory T-cells by 76 d after dose 2
WIBP-CorV: 2 × 5 µg protein doses 3 wks apart; 73%	NAb in 98% by 14 d after dose 2	BAb against whole inactivated virus in 100% at 14 d after dose 2	Not reported

It should be noted that antigen-specific antibodies and TCRs are not directly comparable between vaccines, as specific assays varied

AD adenovirus, *BAb* binding antibodies, *d* day(s), *IFN-γ* interferon-γ, *IL* interleukin, *mo* months, *(N)Ab* (neutralising) antibody/ies, *post-vacc* post-vaccination, *RBD* receptor-binding domain, *S-* SARS-CoV-2 spike, *TCR* T-cell response, *$T_H1/2$* T-helper cell type 1 or 2, *VP* virus particle(s), *wk(s)* week(s), ↓ decrease(d), ↑ increase(d)

[a]Dosages from phase 2/3 trials, all intramuscular injection; adjuvant dosages and excipients not included

[b]Reported efficacy for primary endpoint of prevention of symptomatic COVID-19 infection 7–28 days after scheduled trial dosage regimen

[c]T_H1 bias likely, based on production of IFN-γ, IL-2 and/or tumour necrosis factor, vs T_H2-associated cytokines, e.g. IL-4, 5 and 13

An Indian study (preprint) found the δ variant dominated in breakthrough symptomatic COVID-19 in vaccinated healthcare workers [42]. Relative to wild-type virus, it showed an 8-fold reduction in sensitivity to vaccine-generated Abs. ChAdOx1 recipients had significantly lower serum neutralizing titers against the δ variant than BNT162b2 recipients [42]. However, severe COVID-19 in fully vaccinated people was rare [42]. The β, γ and δ variants seem to reduce convalescent immunity [30].

Other analyses [43–45] suggest VOCs are still susceptible to several vaccines [35, 43–45]. Post-hoc analyses showed the Novavax NVX-CoV2373 vaccine was 86.3% effective against the α variant and 96.4% effective against other variants [35]. A Canadian study (preprint) in > 400,000 people found BNT162b2, mRNA-1273 and ChAdOx1 vaccines provided good protection against VOCs, especially after two doses [45]. Against all VOCs, one dose of mRNA-1273 vaccine provided 72–83% protection, versus 56–66% with BNT162b2 and 48–67% with ChAdOx1. Efficacy in preventing COVID-19 increased to 84–92% with two doses of BNT162b2 or mRNA-1273; there were insufficient data for ChAdOx1 [45].

Table 5 New SARS-CoV-2 (COVID-19) vaccines in phase 2/3 or 3 trials, including those yet to recruit or enrol [2, 5, 30][a]

Companies developing	Vaccine name[a,b]	Trial number, location(s) and comments
DNA or mRNA vaccines		
Abogen Biosciences/Yuxi Walvax Biotechnology (mRNA)	ARCoV	NCT04847102; global; no detail
Arcturus Therapeutics/Duke-NUS Medical School (mRNA)	ARCT-021	NCT05012943; Vietnam
AnGes/Japan Agency for Medical R&D (DNA)	AG0302-COVID19 skin injection	NCT04655625, AG0302-COVID19-JN-02; Japan
Inovio Pharma (DNA)	INO-4800 (intradermal injection then electroporation)	NCT04642638, INNOVATE; multinational
Recombinant viral vector vaccines		
ReiThera SRL/Leukocare Univercells	GRAd-COV2 (1 or 2 doses)	EUCTR2020-005915-39; multinational; in severe disease
		NCT04791423; Italy
AstraZeneca	AZD2816 (nasal spray vaccine tailored to β variant)	NCT04973449; Brazil, UK
Israel Institute for Biological Research/NRx Pharmaceuticals	Brilife	NCT04990466; Brilife studies to be conducted in Israel, Georgia and Ukraine
Inactivated whole virus vaccines		
Beijing Minhai Biotechnology/Shenzhen Kangtai Biological Products	No name	NCT04852705; multinational; no detail; EUA in China
Chinese Academy of Medical Science Institute of Medical Biology	No name	NCT04659239; Brazil, Malaysia
Erciyes University/Health Institutes of Turkey	TURKOVAC	NCT04942405; Turkey; comparative trial vs CoronaVac
Kazakhstan Research Institute for Biological Safety Problems	QazCovid-in®, QazVac	NCT04691908; Kazakhstan; early use in Kazakhstan
Shafa Pharmed Industrial	COVIran, Barekat	IRCT20201202049567N3; Iran; EUA in Iran
Valneva Austria/Dynavax	VLA2001	NCT04864561; UK; comparative trial vs ChAdOx1
Valneva Austria/Dynavax	VLA2101	NCT04956224; New Zealand; one arm in adolescents aged ≥ 12 y, compares Wuhan- (VLA2001) and variant- (VLA2101) based vaccines
Protein subunit vaccines		
Baylor/Texas Children's Hospital, Biological E/Dynavax	BECOV 2, Corbevax	Trial approved by Central Drugs Standard Control Organization - Subject Expert Committee, India [2]
Clover/Dynavax	SCB-2019	NCT04672395 (SPECTRA study); multinational
		PHRR210209-003334; Philippines
Nanogen Biopharma	Nanocovax	NCT04922788; Vietnam
Sanofi Pasteur/GSK	No name	NCT04904549; USA, Honduras, Japan, Africa; 2-stage (monovalent and bivalent vaccines)
Vaxxinity (Covaxx)	UB-612	NCT04683224; no detail (US company)
West China Hospital/West Vac Biopharma	No name (3 doses)	NCT04904471; global; no detail
Vector Institute	EpiVacCorona, Aurora-CoV	No details; approved in Turkmenistan, early use in Russia
Medigen Vaccine Biologics Corp.	MVC-COV1901	NCT05011526; Paraguay; compared with AZD1222; EUA in Taiwan
Cinnagen/Vaxine	Spikogen	NCT05005559; Iran
Livzon Pharmaceutical Group/Institute of Biophysics (Chinese Academy of Sciences)	V-01	Phase 3 trial in Philippines; no details
Plant-based virus-like particle		
Medicago/GSK	CoVLP	NCT04636697; Brazil, Canada, UK, USA

EUA emergency use authorisation

[a]Excludes new trials in vaccines with published phase 3 results and/or World Health Organisation emergency use listing

[b]Dosage regimen is 2 x intramuscular injections and versus placebo, unless otherwise stated

The pattern of results was similar, albeit with slightly better efficacy, in two earlier Qatar studies of BNT162b2 [43] and mRNA-1273 [44] against α and β strains. The efficacy of BNT162b2 against the β variant was about 20% lower than that reported against other strains and both vaccines

provided > 90% protection against severe COVID-19 [44, 46].

Vaccines in development may be more accessible

There are many COVID-19 vaccines in early-stage trials and Table 5 shows those registered at phase 3 level at 7 September [2, 5, 30]. These studies, if successful, may overcome some of the cost, VOC, logistical and other problems that will otherwise limit global access to effective COVID-19 vaccines [8]. Several companies have registered comparative trials, with placebo-controlled trials becoming less feasible as effective vaccines become more widely available, and some are targeting VOCs (Table 5). Among other areas of investigation are differing vaccines for doses one and two (which may be a reasonable and feasible strategy, although further research is needed [47]), and needle-free vaccines [2].

Take home messages

- The global spread of SARS-CoV-2 and resultant COVID-19 pandemic has spawned the rapid development of effective vaccines.
- The six vaccines with WHO EULs are effective, especially against severe COVID-19, but barriers to their global use, such as cost, formulation and storage, mean EULs for other vaccines with good, published phase 3 trial results are urgently needed.
- SARS-CoV-2 mutates rapidly and vaccines must be effective against several highly transmissible VOCs; current indications are that vaccines still prevent severe COVID-19 when VOCs are prevalent.
- All understanding of COVID-19 and vaccines, especially safety and immunogenicity, is short-term and incomplete, limiting the scope for vaccine optimisation.

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